REMARKS

Claims 113 to 127, 129 to 135 and 142 to 144 are pending in this application. Claims 113, 114, 124, 131 and 144 have been amended. Claim 114 has been amended to correct a typographical error. Claim 128 has been canceled and incorporated into claim 124. Claim 131 has been amended to delete subject matter drawn to non-elected inventions. The amendments to claims 113 and 144 are discussed below. Claims 1 to 112 and 136 to 141 have been canceled as being drawn to non-elected inventions. Applicants reserve the right to pursue some or all of these claims in a continuation application(s). New claims 145 to 149 have been added. Support for the recitation in claims 145, 147 and 149 that the CDR-H2 comprises residues 50-65 of SEQ ID NO:27 can be found, *inter alia*, in Figure 6 of the application as filed, and on page 52, lines 24-26 of the application as amended. SEQ ID NO:27 represents the sequence for the gH7 heavy chain.

No new matter is added by any of the foregoing amendments to the specification and the claims.

Objection to the Specification

The specification has been objected to for improper disclosure of amino acid sequences and/or nucleotide sequences without a respective sequence identifier. Applicants have amended the specification on pages 19, 22, 48, and 50 to 52 to add sequence identifiers in the discussion of Figures 2 to 6, 10, and 16. Support for the amendments can be found in the figures and the original sequence listing as filed.

Applicants have amended the specification on page 19 to add new sequence identifiers, SEQ ID NOS: 52-61, for the oligonucleotides presented in Figure 13 as filed. Concurrently with this Amendment and Response, applicants are submitting a substitute paper copy of the sequence listing, an amendment directing its entry into the specification, a computer readable form of the sequence listing, and a statement that the content of the paper and computer readable copies are the same.

Applicants have amended the specification on page 52 to correct typographical errors to change "CDR-H3 (gH5 and gH7)" to "CDR-H2 (gH6 and gH7)". Support for this amendment

can be found in Figure 6 as filed. Figure 6 shows that the CDR-H2s of gH6 and gH7 included the three additional human residues at the end.

No new matter is added to the specification by any of the foregoing amendments.

Objections to the Claims

Claim 113 has been objected to as being drawn to a method of treating a subject with a proliferative disorder comprising administering a therapeutically effective dose of the composition of claim 91. However, the Office Action sets forth that claim 91 is drawn to a non-elected invention. In response, applicants have incorporated the composition features of claim 91 into claim 113, thereby overcoming this objection.

Claim 131 has been objected to for reciting a series of bioactive agents such as growth factors, hormones, cytokines and anti-hormones, which are non-elected inventions. Applicants have amended claim 131 to delete the non-elected inventions, thereby overcoming this objection.

Rejections Under 35 USC §112, First & Second Paragraphs

Claim 144 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for reciting the term CMC-544 as the sole means of identifying the claimed molecule. Although applicants have defined the term CMC-544 in the specification, in the interest of expediting prosecution, claim 144 has been amended to change "CMC-544" to "G5/44-NAc-gamma-calicheamicin DMH AcBut conjugate". Support for this amendment can be found on page 6, lines 28-29, page 22, lines 25-27, page 23, lines 7-16, page 28, lines 11-16, page 31, lines 25-27, page 33, lines 11-14, Examples 2-3 and Figure 17. By reason of the foregoing, applicants respectfully submit that claim 144 is definite under 35 U.S.C. §112, second paragraph.

Claims 113 to 123 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that only an anti-CD22 antibody meets the written description provision of §112, first paragraph. Claim 113 is the independent claim. Applicants respectfully disagree with this rejection and the Examiner's

reasons in support thereof. However, in the interest of expediting prosecution, applicants have amended claim 113 to include the feature of an anti-CD22 antibody, thereby overcoming the rejection as to claim 113. Applicants submit that claims 114 to 123 depend from claim 113 and therefore meet the written description provision of §112, first paragraph.

Claims 113 to 123 have been rejected under 35 U.S.C. §112, first paragraph, on the ground that the specification is not enabling for a method of treating any and/or all proliferative disorders comprising administering a therapeutically effective amount of a composition comprising a cytotoxic drug conjugated to any and/or all carriers for the reasons set forth on pages 6 to 11 in the Office Action. The Examiner does state on page six that the specification is enabling for a method of treating cancer comprising administering a therapeutically effective amount of a composition comprising a cytotoxic drug derivative conjugated to an antibody which specifically binds to a tumor cell antigen. Applicants respectfully disagree with this rejection and the Examiner's reasons in support thereof. However, in the interest of expediting prosecution, applicants have amended claim 113 to change the carrier in the monomeric cytotoxic drug derivative/carrier conjugate to an anti-CD22 antibody. The cytotoxic drug derivative/anti-CD22 antibody conjugates employed in the claimed methods have been shown to be effective against B-cell lymphomas in clinical trials (L. Fayad, et al., Blood (2006) 108:abs 2711, "Clinical Activity of the Immunoconjugate CMC-544 in B-Cell Malignancies: Preliminary Report of the Expanded Maximum Tolerated Dose (MTD) Cohort of a Phase 1 Study"; A. Advani et al., Blood (2005) 106:abs 230, "Preliminary Report of a Phase 1 Study of CMC-544, an Antibody-Targeted Chemotherapy Agent, in Patients With B-Cell Non-Hodgkin's Lymphoma (NHL)). The cytotoxic drug derivative/anti-CD22 antibody conjugates employed in the claimed methods have been shown in preclinical studies to be effective in the treatment of chronic inflammatory diseases such as collagen-induced arthritis and rheumatoid arthritis (K. Dunussi-Joannopoulos et al., Blood (2005) 106:abs 1473; PCT Published Application No. WO/2006 042240). The cytotoxic drug derivative/anti-CD22 antibody conjugates employed in the claimed methods have also been shown in preclinical studies to be effective for the treatment of Non-Hodgkin's B- cell lymphoma when administered in combination with rituximab, an anti-CD20 antibody (see, J. F. DiJoseph et al., Clin. Cancer Res., (2006) 12(1): 242-249; F. J. Hernandez et al., Blood (2005) 106:abs 1473). Applicants note that claims 114 to 123 depend from claim 113. By reason of the foregoing, applicants submit that claims 113 to 123 meet the enablement provision of §112, first paragraph.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejections of the claims under 35 U.S.C. § 112, first and second paragraphs.

Rejections Under 35 U.S.C. §102(b)

A. First Rejection Under 35 U.S.C. §102(b)

Claims 113 to 116 and 122 to 123 are rejected under 35 U.S.C. §102(b) as being anticipated by Hellstrom et al. (U.S. Patent No. 5,134,075). Specifically, the Examiner states that Hellstrom et al. teach a novel monoclonal antibody which binds strongly to a protein associated with human tumors, and teaches a method of treating human tumors comprising administering a therapeutically effective amount of an antibody in conjunction with an appropriate therapeutic agent, wherein the antibody can be conjugated or linked to a therapeutic agent for delivery of the therapeutic agent to the site of the cancer. What is overlooked is that the antibody described in Hellstrom et al. is specific to the L45 antigen (see, e.g., col. 4, lines 9-24 and cols. 6-7), and that the L45 antibody is not easily internalized, making it preferable to target chemotherapeutic drugs to the tumor cells by coupling the antibody with an enzyme (see, col. 8, line 63 - col. 9, line 4). Claims 113 to 116 and 122 to 123 are directed to methods of treatment of a subject comprising administering to the subject a therapeutically dose of a monomeric cytotoxic drug/carrier conjugate in which the carrier is an anti-CD22 antibody, and in which the conjugate is prepared by the steps set forth in claim 113. Furthermore, the specification states on page 21, lines 25-30, that an essential property of a carrier, preferably an antibody or antibody mimic, is its ability to recognize and bind to an antigen or receptor associated with undesired cells and to be subsequently internalized. Applicants submit that Hellstrom et al. does not teach every element of the claimed invention, and therefore claims 113 to 116 and 122 to 123 are not anticipated under 35 U.S.C. §102(b).

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 113 to 116 and 122 to 123 as anticipated under 35 U.S.C. §102(b).

B. Second Rejection Under 35 U.S.C. §102(b)

Claims 113, 124 to 125, 127, 131 to 134 and 142 are rejected under 35 U.S.C. §102(b) as being anticipated by Ghetie et al. (Blood 1992; 80:2315-2320), as evidenced by Newton et al. (Blood 2001; 97: 528-535). Specifically, the Examiner states that Ghetie et al. teach a method of treating a lymphoma, comprising administering a therapeutically effective amount of a cytotoxic drug/carrier conjugate referred to as RFB4-dgA, where deglycosylated ricin A chain is the cytotoxic drug and the carrier is an antibody directed against the CD22 antigen. The Examiner further states that Ghetie et al. teach a method of treating disseminated Daudi lymphoma by administering a therapeutically effective amount of the RFB4-dgA conjugate with an anti-CD19 antibody. The Examiner cites Newton et al. to show that Daudi lymphoma is a B cell malignancy. However, claim 113 is directed to a method of treatment of a subject comprising administering to the subject a therapeutically effective dose of a monomeric cytotoxic drug/carrier conjugate in which the carrier is an anti-CD22 antibody, and the conjugate is prepared by the steps set forth in claim 113. Ghetie et al. does not teach the steps by which the monomeric cytotoxic drug/carrier conjugate is prepared and therefore does not teach every element of the claimed invention in claim 113.

Claim 124, as amended, incorporates the cytotoxic drugs of canceled claim 128 to claim a method of treating a B-cell malignancy comprising the administration to a patient of a therapeutically effective composition comprising a cytotoxic drug-anti-CD22-antibody conjugate wherein the cytotoxic drug is selected from the group consisting of calicheamicins, thiotepa, taxanes, vincristine, daunorubicin, doxorubicin, epirubicin, actinomycin, authramycin, azaserines, bleomycins, tamoxifen, idarubicin, dolastatins/auristatins, hemiasterlins, maytansinoids, and esperamicins. Claims 125, 127, 131 to 134 and 142 depend from claim 124. Claim 128 was not rejected by the Examiner as anticipated by Gehtie et al., because none of these cytotoxic drugs are described in Gehtie et al. Additionally, Gehtie et al. does not teach that the antibody to be administered with the cytotoxic drug-anti-CD22-antibody conjugate can be an anti-CD20 or anti-CD33 antibody as claimed in claim 134. Applicants submit that Gehtie et al. does not teach every element of the claimed methods of treatment, and therefore claims 124 to 125, 127, 131 to 134 and 142 are not anticipated under 35 U.S.C. §102(b).

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 113, 124 to 125, 127, 131 to 134 and 142 as anticipated under 35 U.S.C. §102(b).

C. Third Rejection Under 35 U.S.C. §102(b)

Claims 113 to 121, 124 to 127, 131 to 134 and 142 are rejected under 35 U.S.C. §102(b) as being anticipated by Uhr et al. (U.S. Patent No. 5,686,072). Specifically, the Examiner states that Uhr et al. teach a method of treating a B cell malignancy, including leukemia and Non-Hodgkin's lymphoma, comprising administering to a patient a therapeutically effective amount of an anti-CD19 antibody and anti-CD22 immunotoxin. The Examiner further states that patients include humans and the combination can be administered intravenously.

Uhr et al. defines an immunotoxin as a conjugate comprising an antibody directed against a specific cell surface molecule that has been coupled to one or more toxin molecules (see, col. 4, lines 40-42). In regard to the toxin components of the immunotoxin, Uhr et al. states that included in the term "toxin" are the commonly designated toxins such as poisonous lectins, ricin, abrin, modeccin, botulina and diphtheria toxins, as well as other toxic agents such as radio-isotopes, cytotoxic and carcinostatic drugs and combinations of the various toxins that could also be coupled to one antibody molecule (see, col. 4, line 67 - col. 5, line 6). Preferred toxin components for use in Uhr et al. are the A chain portions of the above toxins, with ricin A chain being particularly preferred, and deglycosylated ricin A chain being even more particularly preferred (see, col. 5, lines 7-10).

Claims 113 to 121 are directed to a method of treatment of a subject comprising administering to the subject a therapeutically effective dose of a monomeric cytotoxic drug/carrier conjugate in which the carrier is an anti-CD22 antibody, and the conjugate is prepared by the steps set forth in claim 113. Uhr et al. does not teach the steps by which the monomeric cytotoxic drug/carrier conjugate is prepared and therefore does not teach every element of the claimed inventions in claims 113 to 121.

Claim 124, as amended, incorporates the cytotoxic drugs of canceled claim 128 to claim a method of treating a B-cell malignancy comprising the administration to a patient of a therapeutically effective composition comprising a cytotoxic drug-anti-CD22-antibody conjugate wherein the cytotoxic drug is selected from the group consisting of calicheamicins, thiotepa, taxanes, vincristine, daunorubicin, doxorubicin, epirubicin, actinomycin, authramycin, azaserines, bleomycins, tamoxifen, idarubicin, dolastatins/auristatins, hemiasterlins, maytansinoids, and esperamicins. Claims 125, 127, 131 to 134 and 142 depend from claim 124. Claim 128 was

not rejected by Examiner as anticipated by Uhr et al. because none of these cytotoxic drugs are described in Uhr et al. Additionally, Uhr et al. does not teach that the antibody to be administered with the cytotoxic drug-anti-CD22-antibody conjugate can be an anti-CD20 or anti-CD33 antibody as claimed in claim 134. Applicants submit that Uhr et al. does not teach every element of the claimed invention, and therefore claims 113 to 121, 124 to 127, 131 to 134 and 142 are not anticipated under 35 U.S.C. §102(b).

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 113 to 121, 124 to 127, 131 to 134 and 142 as anticipated under 35 U.S.C. §102(b).

D. Fourth Rejection Under 35 US.C. §102(b)

Claims 113 to 121, 124 to 127, 131 to 134 and 142 are rejected under 35 U.S.C. §102(b) as being anticipated by Goldenberg (U.S. Patent No. 6,183,744 (applicants note that the Office Action cites the Goldenberg patent as U.S. Patent No. 6,183,477, which applicants believe is a typographical error)).

The Examiner states that Goldenberg teaches a method of treating a B cell malignancy in a patient comprising a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent, citing column 4, lines 25-26 and column 11, lines 5-8. The Examiner states next that Goldenberg teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (col. 11, lines 11-14), and that the immunoconjugates are useful for the treatment of chronic lymphatic leukemias and acute lymphatic leukemias (col. 11, lines 8-11). The Examiner further states that regarding the therapeutic agent of the immunoconjugate, Goldenberg teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes and folic acid analogs. No enediyne compounds, such as calicheamicin, are mentioned in Goldenberg. The Examiner also notes that Goldenberg teaches that the immunoconjugates can be administered intravenously (col. 14, lines 8-15).

The Examiner then proceeds to state that Goldenberg teaches that the immunoconjugate can be administered in combination with another biological agent or chemotherapeutic regimen, such as in combination with an anti-CD19 or anti-CD20 antibody or administered in combination with chemotherapeutic regimes for treatment of intermediate grade Non-Hodgkin's lymphoma (citing col. 13, lines 29-63). This is a mistaken reading of Goldenberg by the Examiner. An immunoconjugate is defined by Goldenberg as a conjugate of an antibody component with a therapeutic agent (see, col. 4, lines 25-26). In column 11, lines 5-7, Goldenberg states that preferred immunoconjugates include radiolabeled antibody components or conjugates of an anti-CD22 antibody component and an immunomodulator. Goldenberg elaborates on the therapeutic immunoconjugates that comprise an immunomodulator in column 11, lines 41-53. The immunoconjugate described by Goldenberg in column 11, lines 41-53, is a conjugate of an antibody component, preferably an anti-CD22 component, and an immunomodulator, where the immunomodulator is a cytokine, stem cell growth factor, lymphotoxin, hematopoietic factor, colony stimulating factor, granulocyte macrophage-colony stimulating factor, or an interferon (see, col. 11, lines 5-6 and 41-53). Cytotoxic drugs are not included in the definition of immunomodulator in Goldenberg.

Turning to Goldenberg's discussion in column 13, Goldenberg clearly states that the subjects receive "naked anti-CD22 antibodies," not immunoconjugates, supplemented with administration of anti-CD19 naked antibodies or anti-CD19 immunoconjugates, or anti-CD20 naked antibodies or anti-CD20 immunoconjugates (see col. 13, lines 29-33). Alternatively, the subjects receive "naked anti-CD22 antibodies," not immunoconjugates, and standard cancer chemotherapy (see col. 13, lines 41-43). The rest of the discussion cited by the Examiner in column 13, lines 41-63, is a discussion of the different chemotherapeutic agents that can be used in combination with the naked anti-CD22 antibodies. The Examiner concedes that Goldenberg does not explicitly teach that calicheamicin can be the therapeutic agent, as in the conjugates employed in the claimed methods of treatment. Goldenberg clearly does not teach every element of the claimed methods of treatment in which therapeutically effective amounts of cytotoxic drug-anti-CD22-antibody conjugate compositions or monomeric calicheamicin derivative/anti-CD22 antibody conjugates are administered to patients. Applicants respectfully submit that Goldenberg does not anticipate the claimed methods of treatment of claims 113 to 121, 124 to 127, 131 to 134 and 142.

Furthermore, claims 113 to 121 are directed to methods of treatment of a subject comprising administering to the subject a therapeutically effective dose of a monomeric cytotoxic drug/carrier conjugate in which the carrier is an anti-CD22 antibody, and the conjugate is prepared by the steps set forth in claim 113. Goldenberg does not teach the steps by which the monomeric cytotoxic drug/carrier conjugate is prepared and therefore does not teach every element of the claimed inventions in claims 113 to 121. Goldenberg clearly does not anticipate the methods of treatment of claims 113 to 121.

With respect to claims 131 to 134, Goldenberg's definitions of an immunoconjugate do not teach or suggest the cytotoxic drug-anti-CD22 antibody conjugate compositions that are administered to patients in the methods of treatment of claims 131 to 134. Furthermore, Goldenberg does not teach that an immunoconjugate can be administered in combination with an antibody, in particular an antibody selected from a group consisting of anti-CD19, anti-CD20 and anti-CD33 antibodies. The only combinations with an antibody taught by Goldenberg is the treatment of subjects with naked anti-CD22 antibodies supplemented with administration of either anti-CD19 or anti-CD20 naked antibodies or anti-CD19 or anti-CD20 immunoconjugates (see col. 13, lines 29-33). Goldenberg does not teach the methods of treatment employing the composition of the cytotoxic drug derivative-anti-CD22 antibody conjugate with an antibody or with an antibody selected from a group consisting of anti-CD19, anti-CD20 and anti-CD33 antibodies. Goldenberg does not teach every element of the claimed methods of treatment of claims 131 to 134 and therefore does not anticipate the methods of treatment of claims 131 to 134.

With respect to claim 142, Goldenberg's definitions of an immunoconjugate do not teach or suggest the cytotoxic drug-anti-CD22 antibody conjugate compositions that are administered to patients in the method of treatment of claim 142. Furthermore, Goldenberg does not teach or suggest that an immunoconjugate can be administered in combination with an antibody and one or more combinations of cytotoxic agents as a part of a treatment regimen. The only combination treatments taught by Goldenberg are the treatment of subjects with naked anti-CD22 antibodies supplemented with administration of either anti-CD19 or anti-CD20 naked antibodies or anti-CD19 or anti-CD20 immunoconjugates (see col. 13, lines 29-33), or the treatment of subjects with naked anti-CD22 antibodies and standard cancer chemotherapy (see, col. 13, lines 41-63). Goldenberg does not teach the methods of treatment employing the composition of the cytotoxic drug derivative-anti-CD22 antibody conjugate with an antibody and

one or more combinations of cytotoxic agents as part of a treatment regimen. Goldenberg does not teach every element of the claimed method of treatment of claim 142 and therefore does not anticipate the method of treatment of claim 142.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 113 to 121, 124 to 127, 131 to 134 and 142 as anticipated under 35 U.S.C. §102(b).

Rejections under 35 U.S.C. §103(a)

Claims 128 to 130 and 143 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Goldenberg (U.S. Patent No. 6,183,744 (applicants note that the Office Action cites the Goldenberg patent as U.S. Patent No. 6,183,477, which applicants believe is a typographical error)) in view of Trail et al. (Current Opinion in Immunology 1999, 11: 584-588). Claim 134 has been rejected under 35 U.S.C. §103(a) as being unpatentable over Goldenberg (U.S. Patent No. 6,183,744 (applicants note that the Office Action cites the Goldenberg patent as U.S. Patent No. 6,183,477, which applicants believe is a typographical error)) in view of Maloney et al. (Blood 1997, 90:2188-2195).

Applicants submit that dependent claims 128 to 130 depend from non-rejected base claim 124. (Applicants wish to point out that non-rejected base claim 124 has been amended to incorporate claim 128, now canceled.) Likewise, dependent claim 134 depends from non-rejected base claim 124. Because independent claim 124 has not been rejected by the Examiner as obvious under 35 U.S.C. §103(a), and claims 128 to 130 and 134 depend from claim 124 and incorporate all of the elements of claim 124, applicants respectfully submit that the rejections of claims 128 to 130 and of claim 134 are therefore improper, and request the Examiner to reconsider and withdraw the rejection of these claims as obvious under 35 U.S.C. §103(a).

Turning to the rejection of independent claim 143, as well as to claims 128 to 130 and 134 that depend from claim 124, the Examiner states that the primary reference, Goldenberg, teaches a method of treating a B cell malignancy in a patient comprising a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent, citing column 4, lines 25-26 and

column 11, lines 5-8. The Examiner states next that Goldenberg teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (column 11, lines 11-14), and that the immunoconjugates are useful for the treatment of chronic lymphatic leukemias and acute lymphatic leukemias (column 11, lines 8-11). The Examiner further states that regarding the therapeutic agent of the immunoconjugate, Goldenberg teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes and folic acid analogs. No enediyne compounds, such as calicheamicin, are mentioned in Goldenberg.

The Examiner then proceeds to state that Goldenberg teaches that the immunoconjugate can be administered in combination with another biological agent or chemotherapeutic regimen, such as in combination with an anti-CD19 or anti-CD20 antibody or administered in combination with chemotherapeutic regimes for treatment of intermediate grade Non-Hodgkin's lymphoma (citing col. 13, lines 29-63). This is a mistaken reading of Goldenberg by the Examiner. An immunoconjugate is defined by Goldenberg as a conjugate of an antibody component with a therapeutic agent (see, col. 4, lines 25-26). In column 11, lines 5-7, Goldenberg states that preferred immunoconjugates include radiolabeled antibody components or conjugates of an anti-CD22 antibody component and an immunomodulator. Goldenberg elaborates on the therapeutic immunoconjugates that comprise an immunomodulator in column 11, lines 41-53. The immunoconjugate described by Goldenberg in column 11, lines 41-53, is a conjugate of an antibody component, preferably an anti-CD22 component, and an immunomodulator, where the immunomodulator is a cytokine, stem cell growth factor, lymphotoxin, hematopoietic factor, colony stimulating factor, granulocyte macrophage-colony stimulating factor, or an interferon (see, col. 11, lines 5-6 and 41-53). Cytotoxic drugs are not included in the definition of immunomodulator in Goldenberg.

Turning to Goldenberg's discussion in column 13, Goldenberg clearly states that the subjects receive "naked anti-CD22 antibodies," not immunoconjugates, supplemented with administration of anti-CD19 naked antibodies or anti-CD19 immunoconjugates, or anti-CD20 naked antibodies or anti-CD20 immunoconjugates (see col. 13, lines 29-33), or the subjects receive "naked anti-CD22 antibodies," not immunoconjugates, and standard cancer chemotherapy (see col. 13, lines 41-43). The rest of the discussion cited by the Examiner in column 13, lines 41-63, is a discussion of the different chemotherapeutic agents that can be

used in combination with the naked anti-CD22 antibodies. The Examiner concedes that Goldenberg does not explicitly teach that the therapeutic agent can be calicheamicin as in the conjugates employed in the methods of claims 128 to 130, 134 and 143. Goldenberg clearly does not teach or suggest the cytotoxic drug-anti-CD22-antibody conjugate compositions that are administered to patients in the claimed methods of treatment. Applicants respectfully submit that Goldenberg, alone or in combination with Trail et al. or Maloney et al. discussed below, does not teach or suggest the claimed methods of treatment in which therapeutically effective amounts of cytotoxic drug-anti-CD22 antibody conjugate compositions or monomeric calicheamicin derivative/anti-CD22 antibody conjugate compositions are administered to patients.

The Examiner states that the Trail et al. article teaches monoclonal antibody drug conjugates in the treatment of cancer. The Examiner further states that specifically, the reference teaches that members of the enediyne family of antibiotics such as calicheamicin are among the most toxic antitumor compounds described to date, but their utility as antitumor drugs has for the most part been limited by their low therapeutic index. Finally, the Examiner states that this cited reference further teaches that antibody directed delivery provides a potential means to exploit the potency of these compounds while minimizing their systemic toxicity [emphasis added]. Applicants respectfully submit that the Trail et al. article merely provides for a "suggestion to try" with its statement that antibody directed delivery provides a potential means without any further elaboration, but does not actually provide motivation to make the cytotoxic drug-anti-CD22 antibody conjugate compositions or monomeric calicheamicinderivative/anti-CD22 antibody conjugate compositions that are administered to patients in the claimed methods of treatment.

With respect to the rejection of claim 134 under 35 U.S.C. § 103(a) as being unpatentable over Goldenberg in view of Maloney et al. (Blood 1997, 90:2188-2195), the Examiner repeats the aforesaid teachings of Goldenberg and states that Maloney et al. teach a method of treating low-grade Non-Hodgkin's lymphoma by administering to a patient a therapeutically effective amount of rituximab, an anti-CD20 antibody, citing the abstract. The Examiner concedes that Goldenberg does not explicitly teach that the immunoconjugate is administered in combination with rituximab.

As discussed above, Goldenberg's definitions of an immunoconjugate do not teach or suggest the cytotoxic drug-anti-CD22 antibody conjugate compositions that are administered to patients in the claimed method of treatment of claim 134. Furthermore, Goldenberg does not teach or suggest that an immunoconjugate can be administered in combination with an antibody, in particular an antibody selected from a group consisting of anti-CD19, anti-CD20 and anti-CD33 antibodies. The only combination with an antibody taught by Goldenberg is the treatment of subjects with naked anti-CD22 antibodies supplemented with the administration of either anti-CD19 or anti-CD20 naked antibodies or anti-CD19 or anti-CD20 immunoconjugates (see col. 13, lines 29-33). Goldenberg does not teach or suggest the method of treatment employing the composition of the cytotoxic drug derivative-anti-CD22 antibody conjugate with an antibody selected from a group consisting of anti-CD19, anti-CD20 and anti-CD33 antibodies, and Maloney et al. does not supply the necessary teachings, alone or when combined with Goldenberg.

The Examiner argues that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Goldenberg and Trail et al. or Maloney et al. to create methods of treatment of B-cell malignancy or aggressive lymphomas in which a patient is administered a therapeutically effective composition comprising a cytotoxic drug-anti-CD22-antibody conjugate alone or with an antibody, including an anti-CD19, anti-CD20 or anti-CD33 antibody. The Examiner states that one would have been motivated to do so because Goldenberg purportedly teaches anti-CD22 immunoconjugates administered to patients alone or in combination with another biological agent, and Trail et al. teaches that antibody-directed delivery of calicheamicin, a potent antibiotic, provides a potential means to exploit its impressive potency while minimizing its systemic toxicity. The Examiner also states that one would have been motivated to do so because Goldenberg purportedly teaches anti-CD22 immunoconjugates administered to patients alone or in combination with another biological agent, and Maloney et al. teaches a method of treatment of Non-Hodgkin's lymphoma by administering an anti-CD20 antibody. The Examiner further states that it is obvious to combine Goldenberg's immunoconjugate, which does not encompass the conjugate compositions used in the claimed methods of the present invention, with Maloney's anti-CD20 antibody, because each has been taught in the prior art for the treatment of lymphoma. The Examiner's assumption of obviousness to combine the methods of Goldenberg and Maloney et al. is undercut by the Examiner's reliance on the review article by Nagahiro Saijo in Cancer

Science, 95(10):772-776 (2004) to support the Examiner's position earlier in the Office Action on the unpredictability of success for molecular-target-based drugs and their combinations.

Applicants submit that to establish a *prima facie* case of obviousness, there must be:

1. some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

2. a reasonable expectation of success; and

3. the references when combined must teach or suggest all the claim limitations.

See, M.P.E.P. § 2143. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter,* 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re*

Lee, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The Examiner's statements regarding the disclosure in Goldenberg in view of Trail et al. acknowledge that neither of the references taken alone would teach or suggest all the elements of the compositions and conjugates administered in the claimed methods of treatment. The Office Action requires the combination of Goldenberg and Trail et al. in order to find that the claimed methods are obvious over these cited references, yet the combination of these two references fails to teach all the limitations of the claimed inventions, fails to provide motivation for one of ordinary skill in the art to combine these references, and fails to provide a reasonable expectation of success. Likewise, the Examiner's statements regarding the disclosure in Goldenberg in view of Maloney et al. acknowledge that neither of the references taken alone would teach or suggest all the elements of the compositions and conjugates administered in the claimed method of treatment. The Office Action requires the combination of Goldenberg and Maloney et al. in order to find that the claimed method is obvious over these cited references, yet the combination of these two references fails to teach all the limitations of the claimed invention, fails to provide motivation for one of ordinary skill in the art to combine these references, and fails to provide a reasonable expectation of success.

As stated above, the Office Action concedes that Goldenberg, the primary reference, does not explicitly teach that calicheamicin can be a therapeutic agent, nor does Goldenberg describe methods of treatment comprising administering to patients therapeutically effective amounts of compositions comprising a cytotoxic drug-anti-CD22-antibody conjugate or a monomeric calicheamicin derivative/anti-CD22 antibody conjugate, alone or together with one or more bioactive agents, namely antibodies that may include anti-CD19, anti-CD20 and anti-CD33 antibodies . Neither Trail et al. nor Maloney et al. supply these teachings, as discussed above. Trail et al. merely provides a suggestion to try to make an antibody-targeted drug conjugate. Maloney et al. merely provides a method of treatment of Non-Hodgkin's lymphoma by administering an anti-CD20 antibody. Applicants submit that none of the cited references teach or suggest the methods of treatment of administering to a patient a composition comprising a cytotoxic drug-anti-CD22-antibody conjugate, alone or together with one or more antibodies as described in the present independent claims. As such, even if the teachings of the Goldenberg

and Trail et al. or Maloney et al. references are combined, as attempted by the Examiner, the resulting combinations would still be deficient in teaching or suggesting the claimed subject matter. As such, Goldenberg, taken alone or in combination with Trail et al. or Maloney et al., does not provide a sufficient basis for a section 103(a) rejection of the aforementioned claims.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 128 to 130 and 143 and the rejection of claim 134 as obvious under 35 U.S.C. §103(a).

Nonstatutory Obviousness-type Double Patenting Rejection

Claims 113 and 116 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 48 of copending Application No. 11/221,902. Applicants respectfully disagree for the following reasons and request that the Examiner reconsider and withdraw this rejection of the claims.

Claim 48 of copending Application No. 11/221,902 claims a method for treating a subject having a 5T4-positive cancer, comprising administering to the subject a therapeutically effective amount of an anti-5T4 antibody/drug conjugate comprising a chimeric or humanized anti-5T4 antibody or antibody fragment and a therapeutic agent, which is directly or indirectly bound to the chimeric or humanized anti-5T4 antibody or antibody fragment. In contrast, claims 113 and 116 of the present application are directed to methods of treating a subject with a proliferative disorder comprising administering a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate with reduced low conjugated fraction below 10 percent prepared by the steps set forth in claim 113. None of the process steps set forth in claims 113 and dependent claim 116 are present in claim 48 in copending Application No. 11/221,902.

Copending Application No. 11/221,902 requires the use of an anti-5T4 antibody in the conjugates employed in the method of treatment claimed in claim 48, whereas the present application requires the use of an anti-CD22 antibody in the conjugates employed in the methods of treatment claimed in claims 113 and 116. The anti-5T4 antibody is directed to the human 5T4 antigen, which is expressed in numerous cancer types, including carcinomas of the bladder, breast, cervix, endometrium, lung, esophagus, ovary, pancreas, stomach, and testes

(see, pages 2 to 4 of Application No. 11/221,902). The anti-CD22 antibody is directed to the CD22 antigen, which is prevalent on certain human lymphomas, and which is over-expressed on most B-cell lymphomas (see, pages 22-23 of the present application). The anti-5T4 antibodies and the anti-CD22 antibodies are patentably distinct, and, likewise, methods of treatment using cytotoxic drug/anti-5T4 antibody conjugates are patentably distinct from methods of treatment using cytotoxic drug/anti-CD22 antibody conjugates.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 113 and 116 on the ground of nonstatutory obviousness-type double patenting over claim 48 of copending Application No. 11/221,902.

Claims 113 and 116 have also been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 88 and 99 of copending Application No. 11/080,587. Applicants respectfully disagree for the following reasons and request that the Examiner reconsider and withdraw this rejection of the claims.

Claims 88 and 99 of copending Application No. 11/080,587 claim methods of treatment comprising administering a therapeutically effective amount of the composition of claim 21. The composition of claim 21 comprises a conjugate of a calicheamicin-hydrolyzable linker derivative covalently attached to an anti-Lewis Y antibody. In contrast, claims 113 and 116 of the present application are directed to methods of treating a subject with a proliferative disorder comprising administering a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate with reduced low conjugated fraction (LCF) below 10 percent prepared by the steps set forth in claim 113. None of the process steps set forth in claims 113 and dependent claim 116 are present in claims 88 and 99 in copending Application No. 11/080,587.

Copending Application No. 11/080,587 requires the use of an anti-Lewis Y antibody in the conjugates employed in the methods of treatment claimed in claims 88 and 99, whereas the present application requires the use of an anti-CD22 antibody in the conjugates employed in the methods of treatment claimed in claims 113 and 116. The anti-Lewis Y antibody is directed to the Lewis Y antigen, which is expressed in normal tissues, but the level of expression is higher in certain tumor types. The Lewis Y antigen is found on cells of some breast, colon, gastric, esophageal, pancreatic, duodenal, lung, bladder and renal carcinomas and gastric and islet cell

neuroendrocrine tumors (see, page 2, lines 11 to 15 of Application No. 11/080,587). The anti-CD22 antibody is directed to the CD22 antigen, which is prevalent on certain human lymphomas, and which is over-expressed on most B-cell lymphomas (see, pages 22-23 of the present application). The anti-Lewis Y antibodies and the anti-CD22 antibodies are patentably distinct, and, likewise, methods of treatment using cytotoxic drug/anti-Lewis Y antibody conjugates are patentably distinct from methods of treatment using cytotoxic drug/anti-CD22 antibody conjugates. By reason of the foregoing, claims 113 and 116 are patentably distinct from claims 88 and 99 of copending Application No. 11/080,587.

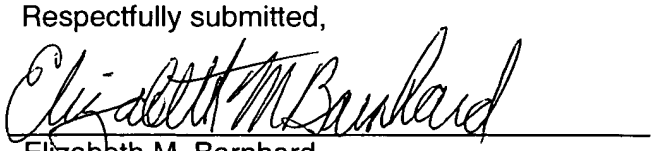
By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims113 and 116 on the ground of nonstatutory obviousness-type double patenting over claims 88 and 99 of copending Application No. 11/080,587.

* * * * *

In view of the foregoing discussion, applicants submit that the present application is in condition for allowance. Reconsideration and allowance are respectfully requested.

If a telephone conference would advance prosecution of this application, the Examiner is invited to telephone the undersigned at (845) 602-1842.

Respectfully submitted,



Elizabeth M. Barnhard
Reg. No. 31,088

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
Tel. No. (845) 602-1842